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Baxter

September 13, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5230 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Federal Register Notice June 28, 1999 (FR Vol 64, No. 123, Pages 34608-25)

Docket No. 99N-0193

Dear Colleague:

Baxter Healthcare Corporation is submitting comments on Proposed Rule 21 CFR Parts 5, 206, 250, 314, 600, and 601 pertaining to regulations on supplements and other changes to an approved application, released for comment on June 28, 1999. General comments are presented first, followed by specific comments.

General Comments:

1. Baxter fully supports the Agency's initiatives to streamline the regulatory process for reporting and implementing post-approval changes, which we believe, will facilitate continuous improvement of pharmaceutical products. However, Baxter does not believe that the reporting recommendations outlined in the proposed rule and the companion guidance will result in significant regulatory relief. Several of the categories recommended will actually result in increased reporting requirements compared to current industry practice. Examples are given in our specific comments.

2. The use of broad or vague terms (i.e., "*any change*" and "*may impact*") should be minimized. Such terms lend themselves to different interpretations, are likely to cause confusion and inconsistent application of the guidance, and are likely to result in more burdensome reporting

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requirements for changes which would be more appropriately categorized as moderate and/or minor changes.

Specific Comments:

§314.3

The proposed rule and the companion guidance define the terms "*validate*" and/or "*validation*" as meaning to assess the effect a change has on the drug and are not intended to mean the same as cGMP validation. We believe that inconsistent use of the same terms for different regulatory meanings lends itself to unnecessary confusion. The terms "*validate*" and "*validation*" should be replaced by "*assess*" and "*assessment*" throughout the proposed rule and companion guidance document.

§314.70(a)(4)

We agree that labeling changes that include important new or revised information concerning product usage and/or safety should be reflected in promotional labeling and advertising in as expedient a time as possible. However, many labeling changes are minor such as those described in current 21 CFR 314.70(d)(2) & (3) and proposed 21 CFR 314.70(d)(2)(x)&(xi) for which prompt revision of associated promotional labeling and/or advertising is not warranted. This position is consistent with current 21 CFR 314.70 which requires prompt revisions of promotional labeling and advertising only for labeling changes described in paragraph (c) but not for those labeling changes described in paragraph (d).

We recommend revising proposed 31 CFR 314.70(a)(4) from "*...in accordance with this section*" to "*...in accordance with paragraphs (b) and (c) of this section*".

§314.70(b)(2)(iii)

The phrase "Changes that may affect product sterility assurance" is too broad and all encompassing. We recommend modification of this phrase to "Changes that may *significantly impact* product sterility assurance".

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§314.70(b)(3)(viii)

Currently, cGMP validation information, including a reference to appropriate SOPs, is required to be submitted in applications only as it pertains to sterilization processes. Proposed section §314.70(b)(3)(viii) implies that a reference to appropriate SOPs is required for all changes, not only those related to a change in sterilization process. We do not believe it is necessary to provide a list of SOPs for any type of change, including a change in sterilization process, and recommend that paragraph 314.70(b)(3)(viii) be deleted in its entirety.

§314.70(c)(2)(i)

"A change in container closure system" is too broad and all encompassing. We recommend changing this sentence to read "A *significant* change in container closure system" for clarity.

§314.70(c)(4)

The last sentence in this paragraph should be changed to read "The information listed in paragraphs (b)(3)(i) through (b)(3)(*vii*)..." for consistency with our comment on §314.70(b)(3)(viii) above.

§314.70(c)(6)(iii)(E)

We believe that any changes made to the labeling that are specifically requested by the FDA should be reportable in the Annual Report.

§314.70(d)(2)(i)

As proposed, we believe this paragraph will increase regulatory reporting requirements over current practice and will result in inconsistent standards for the same products. It is more appropriate and reasonable to use the compendial review and comment process to resolve inconsistencies/differences between compendial and FDA requirements.

We recommend that this paragraph be revised to read "Any change made to comply with an official compendium."

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§314.70(d)(2)(vi)

The proposed wording would result in requirements incremental to current 21 CFR §314.70(b)(2)(ix) and §314.70(d)(5) which do not require that data be from full production batches. We recommend that the phrase "on full production batches" be deleted.

§314.70(d)(3)(iii)

Delete the phrase "and/or SOPs" for consistency with our comment on §314.70(b)(3)(viii) above.

§314.70(e)

There could be circumstances where a comparability protocol(s) is submitted and approved as part of an original application. We recommend changing "Any such protocol, or changes to a protocol, shall be submitted as a supplement..." to "Any such protocol, *if not approved as part of the original application*, or changes to an *approved* protocol, shall be submitted as a supplement..."

Baxter appreciates the opportunity to comment on this Proposed Rule. If you have any questions regarding our comments, please contact Pat Barsanti at (847) 270-4643 or me.

Sincerely,

Marcia Marconi / PSB

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